REMARKS

Claims 1-9 are pending in the Subject Application. In the Office Action of October 23, 2008, claims 1-9 stand rejected. Claim 1 has been amended to recite, "[a] method of controlling self-renewal of a population of human-compatible stem cells by reducing intracellular levels of p18 comprising: delivering small RNA interfering sequences to the human-compatible stem cells for the reduction of p18 levels in the intracellular environment of the stem cells" and finds support in the original claims and throughout the specification, for example, in the "Stimulation of stem cell self-renewal through p18 suppression" section, the "Ongoing studies in human hematopoietic stem cells" section and Figures 12-15 of provisional application 60/620,154 filed October 19, 2004, which was incorporated by reference in the subject application. Claim 6 has been amended to recite, "[t]he method of claim 1, further comprising implanting human-compatible stem cells into a human; wherein the implanted human stem cells are self-renewing" and find support in original claim 6. Claims 4-5 and 9-22 have been canceled. New claims 23-28 have been added and find support throughout the specification, specifically in the sections and figures set forth above.

In addition, the specification has been amended to include several paragraphs from provisional application 60/620,154 filed October 19, 2004, which was incorporated by reference in the Subject Application.

Applicant respectfully submits that no new matter has been introduced by the amendments to the claims and addition of new claims.

A) Objection to Claim 6

Claim 6 has been objected to because of the typographical error "timplant."

Applicant has amended claim 6 to recite "[t]he method of claim 1, further comprising implanting human-compatible stem cells into a human; wherein the implanted human stem cells are self-renewing". Applicant submits that amended claim 6 no longer contains the typographical error "timplant. Accordingly, withdrawal of the objection of claim 6 is respectfully requested.

Hence, Applicant respectfully submits that the objection is obviated and requests that this objection be withdrawn.

B) Rejection of Claims 1-9 under 35 U.S.C. §112, first paragraph

Claims 1-9 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner asserts that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention. The Examiner further asserts that no specific small RNA interfering (siRNA) sequences that are known to down-regulate p18 gene expression are disclosed.

Applicant submits that independent claim 1 and the claims that depend therefrom have been amended to recite, "[a] method of controlling self-renewal of a population of human-compatible stem cells by reducing intracellular levels of p18 comprising: delivering small RNA interfering sequences to the human-compatible stem cells for the reduction of p18 levels in the intracellular environment of the stem cells"

and finds support in provisional application 60/620,154 filed October 19, 2004. Applicant further submits that specific siRNA sequences do not need to be disclosed because one of ordinary skill in the art would know how to design potential siRNA sequences for p18. The designing of siRNA sequences is general knowledge to one of ordinary skill in the art as long as the p18 gene sequence is known and simple siRNA guidelines are followed (*See* http://www.ambion.com/techlib/tb/tb_506.html). The sequence for human p18 has been previously identified (*See* Appendix A), thus, one of ordinary skill in the art would merely need to start at the AUG start codon of the p18 sequence and identify AA dinucleotide sequences. Each AA dinucleotide and the 19 nucleotides that follow could serve as potential siRNA sequence to reduce the level of p18 expression.

In addition, claims 4-5 and 9 have been canceled.

Thus, Applicant submits that sufficient written description has been provided by the amendment to claim 1. Applicant further submits that written description of the siRNA sequences is not necessary because the design of siRNA sequences is general knowledge to one of ordinary skill in the art. Accordingly, withdrawal of the rejection of claims 1-9 under 35 U.S.C. §112, first paragraph is respectfully requested.

Hence, the Applicant respectfully submits that the rejection of claims 1-9 is obviated and requests that this rejection be withdrawn.

C) Rejection of Claims 1-9 under 35 U.S.C. §112, first paragraph

Claims 1-9 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner asserts that the

claims fail to set forth any particular method steps which may be carried out to achieve the desired "control of self-renewal". As set forth in the *Section B*, Applicant submits that claim 1 and the claims that depend therefrom have been amended to recite, "[a] method of controlling self-renewal of a population of human-compatible stem cells by reducing intracellular levels of p18 comprising: delivering small RNA interfering sequences to the human-compatible stem cells for the reduction of p18 levels in the intracellular environment of the stem cells". The amendment to claim 1 finds support, for example, in the "Stimulation of stem cell self-renewal through p18 suppression" section, the "Ongoing studies in human hematopoietic stem cells" section and Figures 12-15 of provisional application 60/620,154 filed October 19, 2004. Thus, Applicant submits that amended claim 1, which is supported by the specification, demonstrates the use of siRNA to reduce intracellular levels of p18 for controlling self-renewal.

In addition, as set forth in *Section B*, the specific siRNA sequences do not need to be disclosed because one of ordinary skill in the art would know how to design potential siRNA sequences for p18 without undue experimentation. Thus, Applicant submits that no specific examples of particular compounds need to be provided to enable claims 1-9.

In addition, the Examiner asserts that one would need to unequivocally determine the precise role of p18 in hematopoietic stem cell differentiation, determine means to modulate the level of p18 protein in hematopoietic stem cells, and determine threshold levels of the p18 protein expression which must be obtained in order to successfully promote reliable self-renewal of the stem cells. Applicant respectfully disagrees. Applicant submits that one of ordinary skill in the art would not need to know

the precise role of p18 in hematopoietic stem cell differentiation, how to modulate levels of p18, or the threshold level of p18 to practice the claimed invention. One of ordinary skill in the art would merely need to reduce the level of p18 using siRNA to practice the claimed invention of controlling self-renewal of a population of human-compatible stem cells.

In addition, the Examiner asserts that that there are no examples in the application, which demonstrate manipulating the level of intracellular p18 in stem cells. Applicant respectfully disagrees. Applicant submits that Figure 12b in provisional application 60/620,154 filed October 19, 2004 shows the reduction of p18 to a 20% expression level when p18 siRNA is used. Thus, Applicant submits that an example of manipulating levels of intracellular p18 is provided.

In addition, claims 4-5 and 9 have been canceled.

Accordingly, Applicant submits that the application provides guidance to one of ordinary skill in the art to practice the claimed invention without having to undertake an undue amount of experimentation. Hence, withdrawal of the rejection of claims 1-9 under 35 U.S.C. §112, first paragraph, is respectfully requested.

D) Rejection of Claims 1-9 under 35 U.S.C. §112, second paragraph

Claims 1-9 are rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential steps. Specifically, the Examiner asserts that steps are omitted to describe what is being done to control self-renewal of the stem cells. As set forth in the *Section B*, Applicant submits that claim 1 has been amended to recite "controlling self-renewal of a population of human-compatible stem cells by reducing

intracellular levels of p18 comprising: delivering small RNA interfering sequences to the human-compatible stem cells for the reduction of p18 levels in the intracellular environment of the stem cell".

Thus, Applicant submits that amended claim 1 and the claims that depend therefrom recites delivering small RNA interfering sequences to the human-compatible stem cells, which in turn reduces the levels of p18 and controls self-renewal of the cells.

In addition, claims 4-5 and 9 have been canceled.

Accordingly, withdrawal of the rejection of claims 1-9 under 35 U.S.C. §112, second paragraph, is respectfully requested.

E) Rejection of Claims 5-9 under 35 U.S.C. §112, second paragraph

Claims 5-9 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, it is not clear how claims 5-9 relate to the method of controlling the self-renewal of stem cells as required by claim 1.

Claim 6 and the claims that depend thereform have been amended for clarity. Amended claim 6 recites, "[t]he method of claim 1, further comprising implanting human-compatible stem cells into a human; wherein the implanted human stem cells are self-renewing". Claims 5 and 9 have been canceled.

Accordingly, withdrawal of the rejection of claims 5-9 under 35 U.S.C. §112, second paragraph, is respectfully requested.

F) Rejection of Claims 1, 2 and 4 under 35 U.S.C. §102(b)

Claims 1, 2 and 4 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by U.S. Patent No. 6,033,847 to Sherr *et al.* (hereinafter "Sherr"). Applicant traverses this rejection for at least the reasons set forth herein.

Amended claim 1 and the claims that depend therefrom recite, "[a] method of controlling self-renewal of a population of human-compatible stem cells by reducing intracellular levels of p18 comprising: delivering small RNA interfering sequences to the human-compatible stem cells for the reduction of p18 levels in the intracellular environment of the stem cells ".

For a reference to be anticipatory under 35 U.S.C. § 102, it is axiomatic that the reference or combination of references teach, either explicitly or inherently, each and every element of the invention as set forth by the claims. Sherr does not teach reducing the levels of p18 to control self-renewal. Instead, Sherr discloses the effect of p18 on cell proliferation. For example, Sherr states:

> [o]ne aspect of the invention is directed to methods of using the proteins of the invention to inhibit the growth of cancer cells and/or to prevent cancer cells from replicating their chromosomal DNA (col. 4, lines 35-38)

Applicant submits that cell proliferation and self-renewal are different terminologies that have distinct biological meanings (*See* page 69 of Appendix B). For example, after its division, a stem cell may pursue various fates, such as, self-maintenance (copying itself), differentiation (becoming another cell type), or apoptosis (cell death). During self-maintenance, cell division occurs. Self-renewal requires cell division to occur. Proliferation also requires cell division to occur, however, proliferation requires a more enhanced level of cell division, which often drives the stem cell toward exhaustion.

Therefore, the result of cell proliferation is often the opposite of self-renewal. Thus, self-renewal and proliferation are not similar processes because they may have opposing outcomes in stem cells.

In addition, Sherr does not teach the use of small RNA interfering sequences. Instead, Sherr discloses the use of antisense oligonucleotides to block p18 expression (*See Abstract*). Applicant submits that small RNA interfering sequences and antisense oligonucleotides are different methodologies with different specificities and efficacies (*See* Appendix C). Thus, Sherr does not teach a method of controlling self-renewal using small RNA interfering sequences in human-compatible stem cells.

In addition, claim 4 has been canceled.

For at least these reasons, Sherr does not anticipate amended claims 1, 2 and 4. Accordingly, Applicant respectfully requests withdrawal of the rejection of claims 1, 2 and 4 under U.S.C. §102(b) over Sherr.

G. New Claims 23-28

New claims 23-28 recite a novel and non-obvious methods of stimulating self-renewal of a population of human compatible stem cells by reducing intracellular levels of p18. The cited reference, Sherr, does not teach or suggest those recited methods of stimulating self renewal.

Thus, Applicant believes that claims 23-28 are patentable in view of the cited prior art. Accordingly, consideration and allowance of new claims 23-28 is respectfully requested.

CONCLUSION

Applicant respectfully submits that claims 1-3, 6-8 and 23-28 recite a novel and non-obvious method of controlling or stimulating self-renewal. Applicant believes that these claims define over the prior art of record and are in proper form for allowance. In view of the foregoing, Applicant respectfully submits that the Subject Application is in condition for allowance. Accordingly, reconsideration of the rejections and allowance of claims 1-3, 6-8 and 23-28 at an early date are earnestly solicited.

Applicant does not otherwise concede, however, the correctness of the rejections with respect to any of the dependent claims not discussed above. Accordingly, Applicant hereby reserves the right to make additional arguments as may be necessary to further distinguish the dependent claims from the cited references based on additional features contained in the dependent claims that were not discussed above. A detailed discussion of these differences is believed to be unnecessary at this time in view of the differences in the claims discussed herein.

Applicant further submits that canceled claims 4-5 and 9-22 may be filed in a subsequent continuation application.

If the undersigned can be of assistance to the Examiner in addressing any additional issues to advance the application to a condition of allowance, please contact the undersigned at the number set forth below.

Respectfully submitted,

June 2, 2009
Date

Sean M. Conrad
Sean M. Conrad, Ph.D.
Patent Agent
Registration No. 61,532

K&L GATES LLP
Henry W. Oliver Building
535 Smithfield Street
Pittsburgh, Pennsylvania 15222
Phone: (412) 355-6218
Fax: (412) 355-6501

Customer No. 26,285

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